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L4 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:678680 CAPLUS
DOCUMENT NUMBER: 139:195197
TITLE: Use of Desert, Indian and Sonic Hedgehog proteins in maintaining intestinal epithelium homeostasis and diagnosis and treatment of gastric and colon cancer
INVENTOR(S): Van Den Brink, Gijs Robert; Peppelenbosch, Maikel Petrus; Hardwick, James Christopher Henry; Van Deventer, Sander Jan Hendrik
PATENT ASSIGNEE(S): Academisch Ziekenhuis Bij De Universiteit Van Amsterdam, Neth.
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

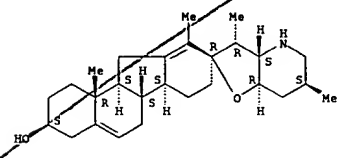
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003070265	A2	20030828	WO 2003-NL127	20030220

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: EP 2002-75690 A 20020220
AB The present invention is based on the key roles played by Desert (Dhh), Indian (Ihh) and Sonic (Shh) Hedgehog proteins in the regulation of homeostasis of the adult intestinal epithelium. Ihh is expressed in the adult mammalian colon and provides a lineage-instructive signal and regulates colonic epithelial morphogenesis in a compartmental fashion. Loss of Ihh expression precedes morphol. change in colon tumorigenesis, i.e. carcinogenesis, and Ihh was absent in HT-29 colon carcinoma cells. Treatment of cancerous HT-29 cells with exogenous Hedgehog protein restored their differentiation. Ihh thus plays a pivotal role in the maintenance of colonic epithelial homeostasis in the differentiation of the GI tract cells and is essential for the enrollment of these GI tract cells on the Death program thus maintaining homeostasis to avoid or treat carcinogenesis. In addn., in gastric cancer expression of Shh is lost and loss of Shh expression precedes morphol. changes in the parietal cells of the stomach. Shh is specifically expressed in fundic glands as well as in gastric heterotopia in the esophagus in Meckel's diverticulum. Shh thus has a unique role as a morphogen in fundic gland homeostasis. The present invention relates to methods in which a source of Hedgehog proteins is used prophylactically or therapeutically to maintain homeostasis of the adult intestinal epithelium. In particular the invention relates methods whereby sources of Hedgehog protein are used to prevent or treat carcinogenesis in adult gastric and colonic tissues. The invention also relates to Hedgehog-based method of diagnosing susceptibility for or the presence of carcinogenesis in the adult GI tract, particularly in gastric

L4 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)
and colonic tissues. The invention further provide for compns. to be used in the Hedgehog-based methods of diagnosing, preventing and treating epithelial tumorigenesis in the adult GI tract.
IT 4449-51-8, Cyclopamine
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of Dhh, Ihh and Shh Hedgehog proteins in maintaining intestinal epithelium homeostasis and diagnosis and treatment of gastric and colon cancer)
RN 4449-51-8 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



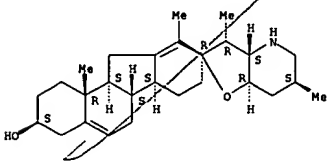
L4 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:793447 CAPLUS
DOCUMENT NUMBER: 137:304813
TITLE: Modulators of hedgehog signaling pathway for treatment of T-cell-mediated diseases
INVENTOR(S): Lamb, Jonathan Robert; Hoyne, Gerard Francis; Dallman, Margaret Jane; Champion, Brian Robert
PATENT ASSIGNEE(S): Lorantis Limited, UK
SOURCE: PCT Int. Appl., 154 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002080952	A2	20021017	WO 2002-GB1666	20020409

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2001-8872 A 20010409
GB 2001-8873 A 20010409
AB Use of a modulator of a Hedgehog signaling pathway, or a modulator of a pathway which is a target of the Hedgehog signaling pathway, in the prepn. of a medicament for treatment of a disease or disorder assocd. with a T-cell mediated disease or disorder.
IT 4449-51-8, Cyclopamine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modulators of hedgehog signaling pathway for treatment of T-cell-mediated diseases)
RN 4449-51-8 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:777728 CAPLUS
DOCUMENT NUMBER: 137:257646
TITLE: Use of cyclopamine in the treatment of basal cell carcinoma and other tumors
INVENTOR(S): Avci, Oktay
PATENT ASSIGNEE(S): Tas, Sinan, Turk.
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002078703	A1	20021010	WO 2001-TR27	20010702
WO 2002078703	C1	20030612		

W: AT, AU, BR, CA, CN, DE, DK, ES, FI, GB, IN, JP, MX, NO, PT, RU, SE, TR, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

WO 2002078704	A1	20021010	WO 2002-TR17	20020419

W: AT, AU, BR, CA, CN, DE, DK, ES, FI, GB, IN, JP, MX, NO, PT, RU, SE, TR, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

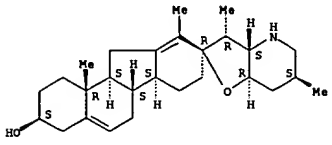
WO 2003088964	A1	20031030	WO 2003-TR17	20030317

W: AT, AU, AZ, BR, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, ID, IN, JP, KR, MX, NO, NZ, PH, PL, PT, RO, RU, SE, TR, UA, US, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR

PRIORITY APPLN. INFO.: WO 2001-TR27 A 20010702
WO 2002-TR17 A 20020419
AB The invention concerns the use of cyclopamine in vivo on basal cell carcinomas to achieve therapeutic effect by causing differentiation of the tumor cells and, at the same time, highly efficient apoptotic death and removal of these tumor cells while preserving the normal tissue cells, including the undifferentiated cells of the normal epidermal basal layer and hair follicles. Causation of apoptosis by cyclopamine is by a non-genotoxic mechanism. These effects make the use of cyclopamine highly desirable in the treatment of basal cell carcinomas and other tumors that use the hedgehog/smoothened signal transduction pathway for proliferation and prevention of apoptosis.
IT 4449-51-8, Cyclopamine
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Use of cyclopamine in the treatment of basal cell carcinoma and other tumors)
RN 4449-51-8 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

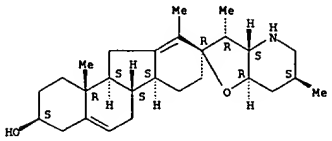
Absolute stereochemistry.

L4 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



IT **4449-51-8D**, Cyclopamine, derivs.
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(Use of cyclopamine in the treatment of basal cell carcinoma and other tumors)
RN 4449-51-8 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

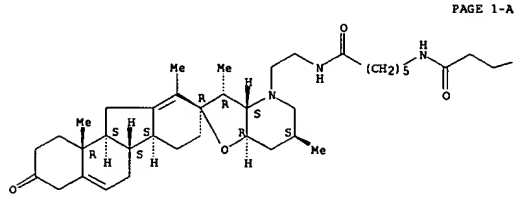


REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)
CN Benzenepropanamide, N-[6-[[2-[(3'R,3'aS,6'S,6aS,6bS,7'aR,2'R,11aS,11bR)-1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-3-oxospiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-4'-yl]ethyl]amino]-6-oxohexyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



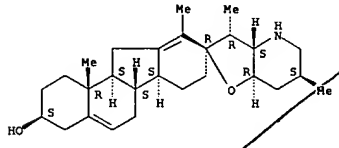
PAGE 1-B

Ph

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:670069 CAPLUS
DOCUMENT NUMBER: 138:248031
TITLE: Medulloblastoma growth inhibition by hedgehog pathway blockade
AUTHOR(S): Berman, David M.; Karhadkar, Sunil S.; Hallahan, Andrew R.; Pritchard, Joel I.; Eberhart, Charles G.; Watkins, D. Neil; Chen, James K.; Cooper, Michael K.; Taipale, Jussi; Olson, James M.; Beachy, Philip A.
CORPORATE SOURCE: Departments of Molecular Biology and Genetics, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Science (Washington, DC, United States) (2002), 297(5586), 1559-1561
CODEN: SCIEAS; ISSN: 0036-8075
PUBLISHER: American Association for the Advancement of Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Constitutive Hedgehog (Hh) pathway activity is assocd. with initiation of neoplasia, but its role in the continued growth of established tumors is unclear. Here, we investigate the therapeutic efficacy of the Hh pathway antagonist cyclopamine in preclin. models of medulloblastoma, the most common malignant brain tumor in children. Cyclopamine treatment of murine medulloblastoma cells blocked proliferation in vitro and induced changes in gene expression consistent with initiation of neuronal differentiation and loss of neuronal stem cell-like character. This compd. also caused regression of murine tumor allografts in vivo and induced rapid death of cells from freshly resected human medulloblastomas, but not from other brain tumors, thus establishing a specific role for Hh pathway activity in medulloblastoma growth.
IT **4449-51-8**, Cyclopamine **306387-90-6**
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(medulloblastoma growth inhibition by hedgehog pathway blockade with cyclopamine in relation to proliferation inhibition, differentiation initiation, and loss of neuronal stem cell-like character)
RN 4449-51-8 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 306387-90-6 CAPLUS

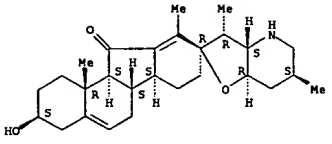
L4 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:293477 CAPLUS
DOCUMENT NUMBER: 136:304056
TITLE: Hedgehog antagonists, methods and uses related thereto
INVENTOR(S): Dudek, Henryk; Pepicelli, Carmen; Karavanov, Irina
PATENT ASSIGNEE(S): Curis, Inc., USA
SOURCE: PCT Int. Appl., 224 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002030462	A2	20020418	WO 2001-US32100	20011015
WO 2002030462	C2	20030515		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002165221	A1	20021107	US 2001-977096	20011012
AU 2001096844	A5	20020422	AU 2001-96844	20011015
PRIORITY APPLN. INFO.:			US 2000-240564P P	20001013
			US 2000-240536P P	20001013
			WO 2001-US32100 W	20011015

AB The present application is directed to compns. and methods for inhibiting angiogenesis and treating or preventing unwanted cell proliferation, including tumors, by inhibiting the hedgehog pathway, e.g., with an antagonist of the hedgehog pathway such as those disclosed herein. In one embodiment, the subject methods may be used to inhibit unwanted cell proliferation by detg. whether cells overexpress a gli gene, and contacting cells that overexpress gli gene with an effective amt. of a hedgehog antagonist. In preferred embodiments ,the unwanted cell proliferation is cancer or benign prostatic hyperplasia. Another aspect of the present invention involves measuring the levels of gli gene expression in order detn. the likelihood that a cancer will develop or to detn. a cancer treatment protocol. Another embodiment of the invention involves methods for using hedgehog antagonists to stimulate surfactant prodn. or lamellated body formation in lung cells, esp. the lung cells of premature infants. In other preferred embodiments, hedgehog antagonists are selected from small mols., hedgehog antibodies, antisense nucleic acids and ribozymes.
IT **469-59-0**, Jervine **4449-51-8**, Cyclopamine
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)
RN 469-59-0 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-11(1H)-one, 2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11a,11b-hexadecahydro-3-hydroxy-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

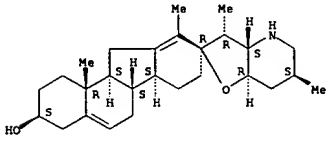
Absolute stereochemistry.

L4 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



RN 4449-51-8 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:507523 CAPLUS
DOCUMENT NUMBER: 135:87198
TITLE: Use of steroidal alkaloids to reverse multidrug resistance
INVENTOR(S): Liscovitch, Mordechai; Lavie, Yaakov
PATENT ASSIGNEE(S): Yeda Research and Development Co. Ltd., Israel
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001049279	A2	20010712	WO 2000-IL866	20001228
WO 2001049279	A3	20021017		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1274445	A2	20030115	EP 2000-983471	20001228
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JP 2003519178	T2	20030617	JP 2001-549647	20001228
US 2003114393	A1	20030619	US 2002-169353	20021104

PRIORITY APPLN. INFO.: IL 1999-133809 A 19991230
WO 2000-IL866 W 20001228

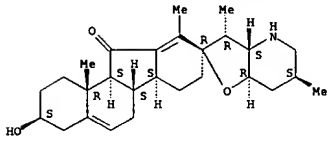
AB The invention provides steroidal alkaloids for inhibiting or reversing multidrug resistance in cancer or in bacterial, fungal or parasitic infections. The steroidal alkaloid may be administered to the patient alone or in combination with an anticancer, antibacterial, antifungal or antiparasitic agent. Examples of steroidal alkaloids include members of the solanidane or spirosolane families (e.g. tomatidine), and C-nor-D-homo steroids, e.g. of the jervane or veratramine families.

IT **469-59-0, Jervine 4449-51-8, Cyclopamine**
14410-98-1 14788-78-4 19773-24-1, Peimisine
24508-94-9, Tetrahydrojervine 212968-58-6, Verapatuline
347842-64-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(steroidal alkaloids for reversal of multidrug resistance)

RN 469-59-0 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-11(1H)-one, 2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11a,11b-hexadecahydro-3-hydroxy-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

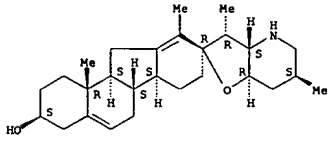
Absolute stereochemistry.

L4 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



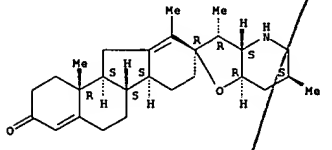
RN 4449-51-8 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 14410-98-1 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3(2H)-one, 1,3'a,4',5,5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-hexadecahydro-3',6',10,11b-tetramethyl-, (2'R,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)- (9CI) (CA INDEX NAME)

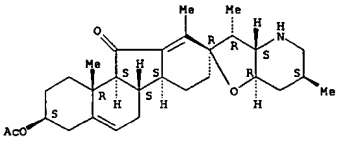
Absolute stereochemistry.



RN 14788-78-4 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-11(1H)-one, 3-(acetyloxy)-2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11a,11b-hexadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

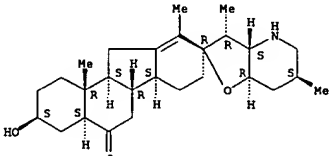
Absolute stereochemistry.

L4 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



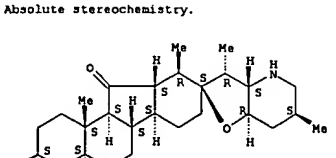
RN 19773-24-1 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-5(6H)-one, 1,2,3,3'a,4,4',4a,5',6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3-hydroxy-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,4aS,6'S,6aR,6bS,7'aR,11aS,11bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 24508-94-9 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-11(1H)-one, eicosahydro-3-hydroxy-3',6',10,11b-tetramethyl-, (2'S,3S,3'R,3'aS,4aS,6'S,6aS,6bS,7'aR,10R,10aS,11aS,11bS)- (9CI) (CA INDEX NAME)

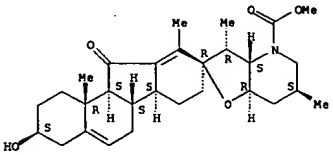
Absolute stereochemistry.



RN 212968-58-6 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridine]-4'(3'aH)-carboxylic acid, 1,2,3,4,5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-hexadecahydro-3-hydroxy-3',6',10,11b-tetramethyl-11-oxo-, methyl ester, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)- (9CI) (CA INDEX NAME)

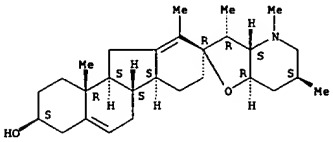
L4 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

Absolute stereochemistry. Rotation (-).

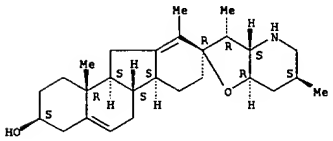


RN 347842-64-2 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',4',6',10,11b-pentamethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:447066 CAPLUS
DOCUMENT NUMBER: 136:210143
TITLE: Inhibitory effect of steroidal alkaloids on drug transport and multidrug resistance in human cancer cells
AUTHOR(S): Lavie, Yaakov; Harel-Orbital, Tovi; Gaffield, William; Liscovitch, Mordechai
CORPORATE SOURCE: Department of Biological Regulation, Weizmann Institute of Science, Rehovot, 76100, Israel
SOURCE: Anticancer Research (2001), 21(2A), 1189-1194
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Intrinsic or acquired resistance of tumor cells to multiple cytotoxic drugs (multidrug resistance, MDR) is a major cause of failure of cancer chemotherapy. MDR is often caused by elevated expression of drug transporters such as P-glycoprotein (P-gp) or multidrug resistance protein (MRP). A no. of compds., termed chemosensitizers, have little or no cytotoxic action of their own, but inhibit (P-gp) or MRP-mediated drug export and are capable of sensitizing MDR cells to the cytotoxic effects of chemotherapeutic drugs. Here the authors examd. the ability of steroidal alkaloids of plant origin, namely the Veratrum sp. alkaloid cyclopamine and the Lycopersicon sp. alkaloid tomatidine, to act as potent and effective chemosensitizers in multidrug resistant tumor cells. Drug uptake was detd. by measuring accumulation of tetramethylrosamine in multidrug resistant NCl AdrR human adenocarcinoma cells. Resistance to adriamycin and vinblastine was detd. by utilizing the MTT cell survival assay. Cyclopamine and tomatidine elevate tetramethylrosamine uptake by NCl AdrR cells and sensitize the cells to the cytotoxic action of adriamycin and vinblastine. In both cases these agents are comparable in patency and efficacy to verapamil, a reversal agent commonly used in MDR research. It is concluded that steroidal alkaloids of plant origin act as inhibitors of P-gp-mediated drug transport and multidrug resistance and therefore may serve as chemosensitizers in combination chemotherapy with conventional cytotoxic drugs for treating multidrug resistant cancer.
IT 4449-51-8, Cyclopamine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitory effect of steroidal alkaloids on drug transport and multidrug resistance in human cancer cells)
RN 4449-51-8 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

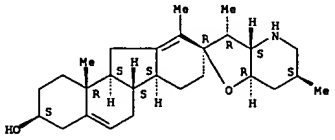
Absolute stereochemistry.

L4 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:434884 CAPLUS
DOCUMENT NUMBER: 135:41031
TITLE: Methods using hedgehog protein or hedgehog protein-encoding nucleic acid to stimulate insulin production by pancreatic .beta.-cells
INVENTOR(S): Habener, Joel F.; Thomas, Melissa K.
PATENT ASSIGNEE(S): The General Hospital Corporation, USA
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001041786	A1	20010614	WO 2000-US33575	20001208
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2003013646	A1	20030116	US 2000-733634	20001208

PRIORITY APPLN. INFO.: US 1999-170282P P 19991210
AB The invention features a method of treating deficiency of insulin in a patient, comprising administering to a patient in need thereof hedgehog protein or nucleic acid in an amt. effective to raise the level of insulin in the patient. A method is also disclosed for suppressing insulin secretion using hedgehog protein inhibitor, e.g. cyclopamine.
IT 4449-51-8, Cyclopamine 4449-51-8D, Cyclopamine, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hedgehog protein or hedgehog protein-encoding nucleic acid to stimulate insulin prodn. by pancreatic .beta.-cells)
RN 4449-51-8 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

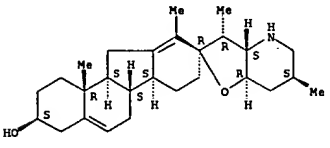
Absolute stereochemistry.



RN 4449-51-8 CAPLUS

L4 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:283977 CAPLUS
DOCUMENT NUMBER: 134:295995
TITLE: Synthesis, compositions and uses of steroidal alkaloids as regulators of the hedgehog pathway
INVENTOR(S): Beachy, Philip A.
PATENT ASSIGNEE(S): Johns Hopkins University School of Medicine, USA
SOURCE: PCT Int. Appl., 164 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001027135	A2	20010419	WO 2000-US28479	20001013
WO 2001027135	A3	20020510		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1235851	A2	20020904	EP 2000-973544	20001013
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003516317	T2	20030513	JP 2001-530353	20001013

PRIORITY APPLN. INFO.: US 1999-159215P P 19991013
US 2000-229273P P 20000830
WO 2000-US28479 W 20001013

OTHER SOURCE(S): MARPAT 134:295995

AB The present invention makes available, inter alia, methods and reagents for modulating smoothened-dependent pathway activation. In certain embodiments, the subject methods can be used to counteract the phenotypic effects of unwanted activation of a hedgehog pathway, such as resulting from hedgehog gain-of-function, ptc loss-of-function or smoothened gain-of-function mutations. Synthesis of cyclopamine, jervine and cycloposine derivs. is presented.

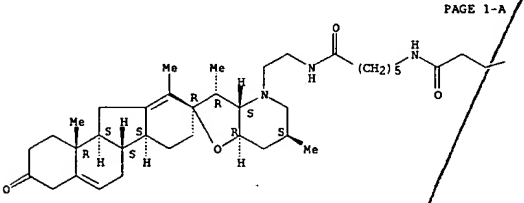
IT **306387-90-6P 334616-24-9P 334616-28-3P**
334616-33-0P 334616-35-2P 334616-36-3P
334616-40-9P 334616-43-2P 334616-45-4P
334616-53-4P 334616-55-6P 334616-56-7P
334616-63-6P 334616-69-2P 334616-70-5P
334616-75-0P 334616-76-1P 334658-24-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis, compns. and uses of steroidal alkaloids as regulators of the hedgehog pathway)

RN 306387-90-6 CAPLUS
CN Benzenepropanamide, N-[6-[[2-[(3'R,3'aS,6'S,6aS,6bS,7'aR,2'R,11aS,11bR)-1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-3-oxospiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-

L4 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)
b]pyridin]-4'-yl]ethyl]amino]-6-oxohexyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



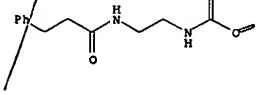
PAGE 1-B

Ph

RN 334616-24-9 CAPLUS
CN Carbamic acid, [2-[(1-oxo-3-phenylpropyl)amino]ethyl]-, (3S,3'R,3'aS,6'S,6aS,6bS,7'aR,2'R,11aS,11bR)-1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethylspiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-yl ester (9CI) (CA INDEX NAME)

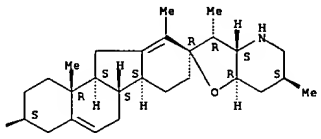
Absolute stereochemistry.

PAGE 1-A



L4 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

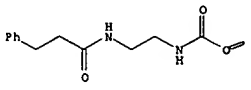
PAGE 1-B



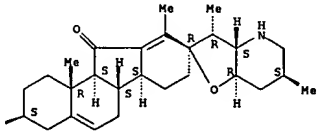
RN 334616-28-3 CAPLUS
CN Carbamic acid, [2-[(1-oxo-3-phenylpropyl)amino]ethyl]-, (3S,3'R,3'aS,6'S,6aS,6bS,7'aR,2'R,11aS,11bR)-1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-11-oxospiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



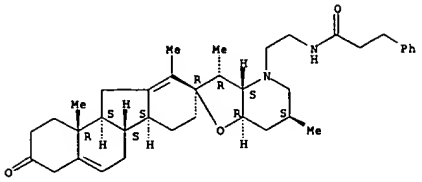
PAGE 1-B



RN 334616-33-0 CAPLUS
CN Benzenepropanamide, N-[2-[(3'R,3'aS,6'S,6aS,6bS,7'aR,2'R,11aS,11bR)-1,2,3,3',3'a,4,5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-3-oxospiro[9H-benzo[a]fluorene-9,2'(4'H)-furo[3,2-b]pyridin]-4'-yl]ethyl]- (9CI) (CA INDEX NAME)

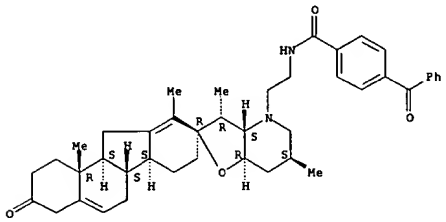
Absolute stereochemistry.

L4 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



RN 334616-35-2 CAPLUS
CN Benzamide, 4-benzoyl-N-[2-[(3'R,3'aS,6'S,6aS,6bS,7'aR,2'R,11aS,11bR)-1,2,3,3',3'a,4,5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-3-oxospiro[9H-benzo[a]fluorene-9,2'(4'H)-furo[3,2-b]pyridin]-4'-yl]ethyl]- (9CI) (CA INDEX NAME)

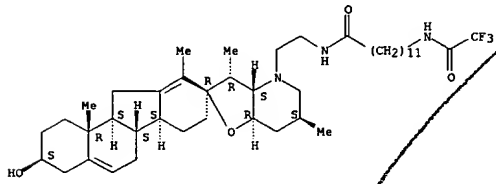
Absolute stereochemistry.



RN 334616-36-3 CAPLUS
CN Benzenepropanamide, 4-azido-3-iodo-N-[2-[(3S,3'R,3'aS,6'S,6aS,6bS,7'aR,2'R,11aS,11bR)-1,2,3,3',3'a,4,5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3-hydroxy-3',6',10,11b-tetramethylspiro[9H-benzo[a]fluorene-9,2'(4'H)-furo[3,2-b]pyridin]-4'-yl]ethyl]- (9CI) (CA INDEX NAME)

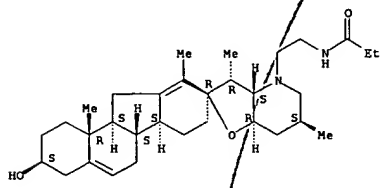
Absolute stereochemistry.

L4 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



RN 334616-45-4 CAPLUS
CN Propanamide, N-[2-[(3S,3'R,3'aS,6'S,6aS,6bS,7'aR,2'R,11aS,11bR)-1,2,3,3',3'a,4,5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3-hydroxy-3',6',10,11b-tetramethylspiro[9H-benzo[a]fluorene-9,2'(4'H)-furo[3,2-b]pyridin]-4'-yl]ethyl]- (9CI) (CA INDEX NAME)

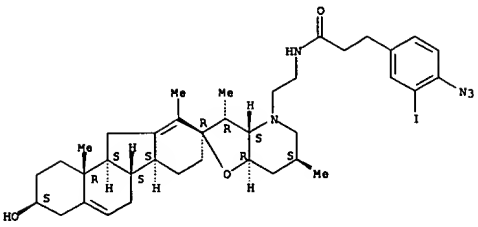
Absolute stereochemistry.



RN 334616-53-4 CAPLUS
CN Benzenepropanamide, 4-azido-3-iodo-N-[6-[[2-[(3S,3'R,3'aS,6'S,6aS,6bS,7'aR,2'R,11aS,11bR)-1,2,3,3',3'a,4,5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3-hydroxy-3',6',10,11b-tetramethylspiro[9H-benzo[a]fluorene-9,2'(4'H)-furo[3,2-b]pyridin]-4'-yl]ethyl]amino]-6-oxohexyl]- (9CI) (CA INDEX NAME)

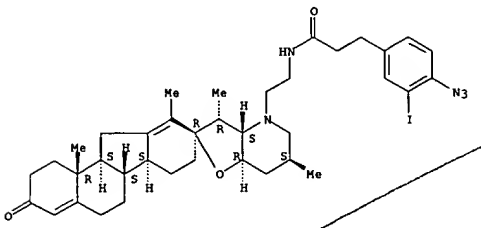
Absolute stereochemistry.

L4 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



RN 334616-40-9 CAPLUS
CN Benzenepropanamide, 4-azido-3-iodo-N-[2-[(3'R,3'aS,6'S,6aS,6bS,7'aR,2'R,11aS,11bR)-1,2,3,3',3'a,5,5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-3-oxospiro[9H-benzo[a]fluorene-9,2'(4'H)-furo[3,2-b]pyridin]-4'-yl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 334616-43-2 CAPLUS
CN Dodecanamide, N-[2-[(3S,3'R,3'aS,6'S,6aS,6bS,7'aR,2'R,11aS,11bR)-1,2,3,3',3'a,4,5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3-hydroxy-3',6',10,11b-tetramethylspiro[9H-benzo[a]fluorene-9,2'(4'H)-furo[3,2-b]pyridin]-4'-yl]ethyl]-12-[(trifluoroacetyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

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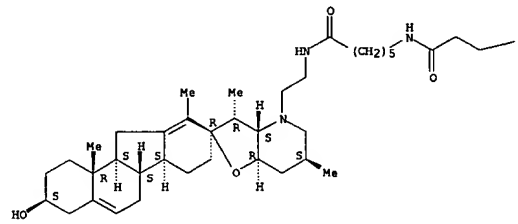

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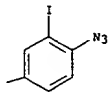

RN 334616-55-6 CAPLUS
CN 1H-Thieno[3,4-d]imidazole-4-pentanamide, hexahydro-N-[6-[[2-[(2'R,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-1,2,3,3',3'a,5,5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-3-oxospiro[9H-benzo[a]fluorene-9,2'(4'H)-furo[3,2-b]pyridin]-4'-yl]ethyl]amino]-6-oxohexyl]-2-oxo-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

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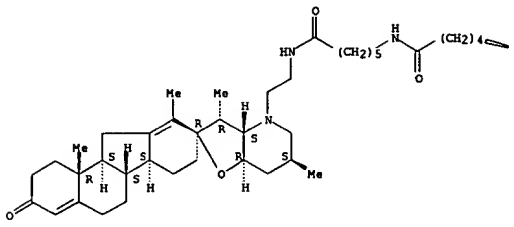
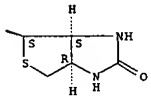
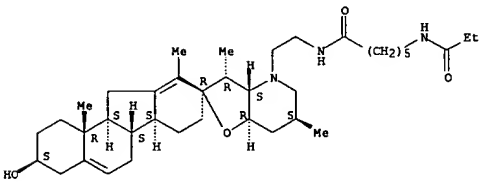


PAGE 1-B



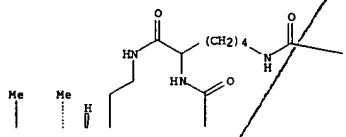
RN 334616-56-7 CAPLUS
CN Hexanamide, N-[2-[(3S,3'R,3'aS,6'S,6aS,6bS,7'aR,2'R,11aS,11bR)-1,2,3,3',3'a,4,5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3-hydroxy-3',6',10,11b-tetramethylspiro[9H-benzo[a]fluorene-9,2'(4'H)-furo[3,2-b]pyridin]-4'-yl]ethyl]-6-[(1-oxopropyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

PAGE 1-A



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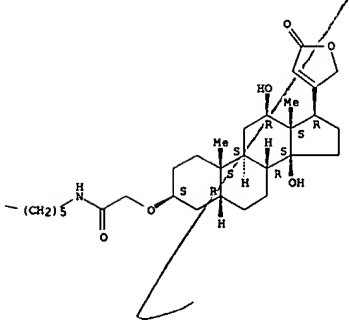
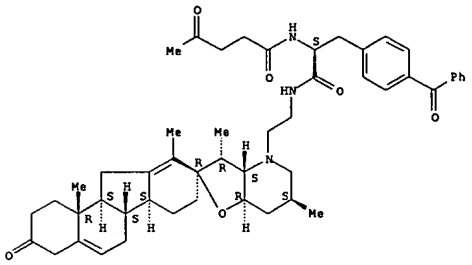


L4 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

RN 334616-63-6 CAPLUS
CN Benzenepropanamide, 4-benzoyl-.alpha.-[(1,4-dioxopentyl)amino]-N-[2-[(3'R,3'aS,6'S,6aS,6bS,7'aR,2'R,11aS,11bR)-1,2,3,3',3'a,4,5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-3-oxospiro[9H-benzo[a]fluorene-9,2'(4'H)-furo[3,2-b]pyridin]-4'-yl]ethyl]-, (.alpha.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 334616-69-2 CAPLUS
CN Card-20(22)-enolide, 3-[2-[(6-[(5-[(4-benzoylbenzoyl)amino]-6-[[2-[(2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-1,2,3,3',3'a,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3-hydroxy-3',6',10,11b-tetramethylspiro[9H-benzo[a]fluorene-9,2'(4'H)-furo[3,2-b]pyridin]-4'-yl]ethyl]amino]-6-oxohexyl]amino]-6-oxohexyl]amino]-2-oxoethoxy]-12,14-dihydroxy-, (3.beta.,5.beta.,12.beta.)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

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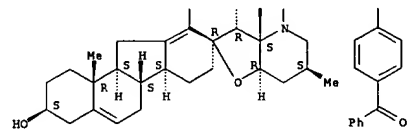
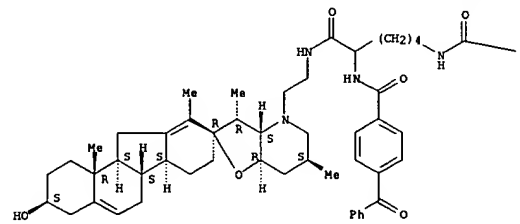


RN 334616-70-5 CAPLUS
CN 1H-Thieno[3,4-d]imidazole-4-pentanamide, N-[6-[[5-[(4-benzoylbenzoyl)amino]-6-[[2-[(2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-1,2,3,3',3'a,4,5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3-hydroxy-3',6',10,11b-tetramethylspiro[9H-benzo[a]fluorene-9,2'(4'H)-furo[3,2-b]pyridin]-4'-yl]ethyl]amino]-6-oxohexyl]amino]-6-oxohexyl]hexahydro-2-oxo-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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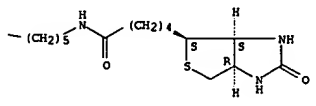

RN 334616-75-0 CAPLUS
CN 1H-Thieno[3,4-d]imidazole-4-pentanamide, N-[6-[[(1S)-1-[(4-benzoylphenyl)methyl]-2-[[6-[[2-[(2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-1,2,3,3',3'a,4,5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3-

L4 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)
hydroxy-3',6',10,11b-tetramethylspiro[9H-benzo[a]fluorene-9,2'(4'H)-furo[3,2-b]pyridin]-4'-yl]ethyl]amino]-6-oxohexyl]amino]-2-oxoethyl]amino]-6-oxohexyl]hexahydro-2-oxo-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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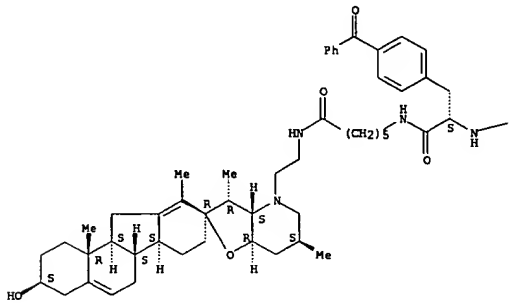

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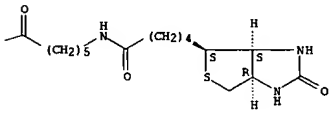

RN 334616-76-1 CAPLUS
CN Benzenepropanamide, 4-azido-3-(iodo-125I)-N-[6-[[2-[(3S,3'R,3'aS,6'S,6aS,6bS,7'aR,2'R,11aS,11bR)-1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3-hydroxy-3',6',10,11b-tetramethylspiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-

L4 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

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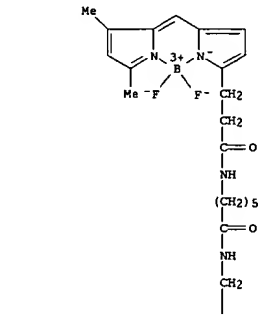

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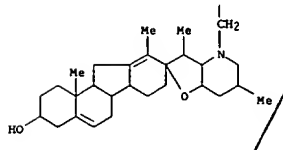

L4 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)
b]pyridin]-4'-yl]ethyl]amino]-6-oxohexyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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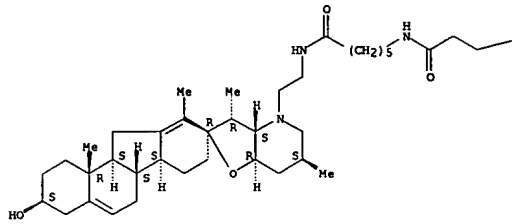

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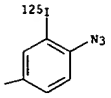


RN 334658-24-1 CAPLUS
CN Boron, [5-[(3,5-dimethyl-2H-pyrrol-2-ylidene-.kappa.N)methyl]-N-[6-[[2-[(3S,3'R,3'aS,6'S,6aS,6bS,7'aR,2'R,11aS,11bR)-1,2,3,3',3'a,4,5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3-hydroxy-3',6',10,11b-tetramethylspiro[9H-benzo[a]fluorene-9,2'(4'H)-furo[3,2-b]pyridin]-4'-yl]ethyl]amino]-6-oxohexyl]-1H-pyrrole-2-propanamidato-.kappa.N1]difluoro-, (T-4)- (9CI) (CA INDEX NAME)

L4 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:880985 CAPLUS
DOCUMENT NUMBER: 134:37058
TITLE: Therapeutic use of an inhibitor of a hedgehog or a hedgehog-related signaling pathway
INVENTOR(S): Lamb, Jonathan Robert; Hoyne, Gerard Francis; Dallman, Margaret Jane
PATENT ASSIGNEE(S): Lorantis Limited, UK
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000074706	A1	20001214	WO 2000-GB2191	20000605
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1183040	A1	20020306	EP 2000-935413	20000605
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003501395T	T2	20030114	JP 2001-501240	20000605
US 2002192216	A1	20021219	US 2001-13310	20011207

PRIORITY APPLN. INFO.: GB 1999-13350 A 19990608
GB 1999-21953 A 19990916
WO 2000-GB2191 W 20000605

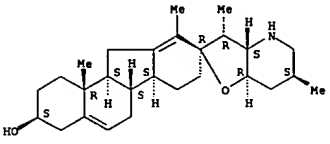
AB Use of an inhibitor of a Hedgehog signaling pathway, or an inhibitor of a pathway which is a target of the Hedgehog signaling pathway in the prepn. of a medicament for treatment of epithelial cell hyperplasia, fibrosis of tissue, inflammation, cancer or an immune disorder. Also a transgenic animal or cell line capable of expressing a component or an inhibitor of a hedgehog signaling pathway or a target pathway of the hedgehog signaling pathway.

IT 4449-51-8, Cyclopamine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic use of inhibitor of hedgehog protein or hedgehog-related signaling pathway and transgenic animal or cell line expressing component or inhibitor of these pathways)

RN 4449-51-8 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)
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Absolute stereochemistry.

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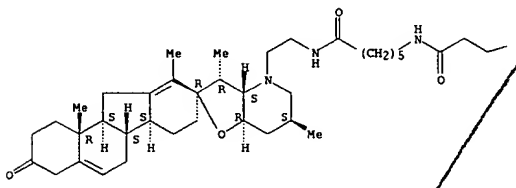

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Ph

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

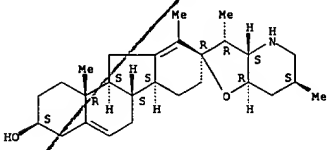
L4 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:637045 CAPLUS
DOCUMENT NUMBER: 133:344307
TITLE: Effects of oncogenic mutations in Smoothened and Patched can be reversed by cyclopamine
AUTHOR(S): Taipale, Jussi; Chen, James K.; Cooper, Michael K.; Wang, Baolin; Mann, Randall K.; Milenkovic, Ljiljana; Scotts, Matthew P.; Beachy, Philip A.
CORPORATE SOURCE: Department of Molecular Biology and Genetics, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Nature (London) (2000), 406(6799), 1005-1009
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Basal cell carcinoma, medulloblastoma, rhabdomyosarcoma and other human tumors are assocd. with mutations that activate the proto-oncogene Smoothened (SMO) or that inactivate the tumor suppressor Patched (PTCH). Smoothened and Patched mediate the cellular response to the Hedgehog (Hh) secreted protein signal, and oncogenic mutations affecting these proteins cause excess activity of the Hh response pathway. Here we show that the plant-derived teratogen cyclopamine, which inhibits the Hh response, is a potential 'mechanism-based' therapeutic agent for treatment of these tumors. We show that cyclopamine or synthetic derivs. with improved potency block activation of the Hh response pathway and abnormal cell growth assocd. with both types of oncogenic mutation. Our results also indicate that cyclopamine may act by influencing the balance between active and inactive forms of Smoothened.

IT 4449-51-8, Cyclopamine 306387-90-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of oncogenic mutations in Smoothened and Patched can be reversed by cyclopamine)

RN 4449-51-8 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 306387-90-6 CAPLUS
CN Benzenepropanamide, N-[6-[[2-[(3'R,3'aS,6'S,6aS,6bS,7'aR,2'R,11aS,11bR)-

L4 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:493313 CAPLUS
DOCUMENT NUMBER: 133:99549
TITLE: Regulation of the hedgehog pathway and smoothened gain-of-function by gene patched agonists
INVENTOR(S): Dudek, Henryk; Ji, Benxiu
PATENT ASSIGNEE(S): Ontogeny, Inc., USA
SOURCE: PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000041545	A2	20000720	WO 2000-US873	20000113
WO 2000041545	A3	20000928		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6291516	B1	20010918	US 1999-417564	19991014
EP 1143961	A2	20011017	EP 2000-906910	20000113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2003517279	T2	20030527	JP 2000-593166	20000113
US 2001034337	A1	20011025	US 2001-867311	20010529

PRIORITY APPLN. INFO.: US 1999-115642P P 19990113
US 1999-119594P P 19990210
US 1999-142124P P 19990702
US 1999-417564 A 19991014
WO 2000-US873 W 20000113

OTHER SOURCE(S): MARPAT 133:99549

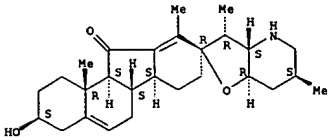
AB The present invention makes available methods and reagents for inhibiting aberrant growth states resulting from hedgehog gain-of-function, patched (ptc) loss-of-function or smoothened gain-of-function comprising contacting a cell with a compd., such as a polypeptide or small mol. in an amt. sufficient to control the aberrant growth state, e.g., to agonize a normal ptc pathway or antagonize smoothened or hedgehog activity. The present invention further makes available methods and reagents for ameliorating the consequences of hedgehog loss-of-function, ptc gain-of-function, or smoothened loss-of-function comprising contacting a cell with a compd., such as a polypeptide or small mol., in an amt. sufficient for amelioration. In certain embodiments, the subject compds., e.g., a cAMP analog, adenylate cyclase agonist, or cAMP phosphodiesterase inhibitor, regulate cAMP levels, which in turn modulates activity of the hedgehog pathway. Thus, compds. such as jervine, cyclopamine, and forskolin analogs are also effective in inhibition of medulloblastoma.

IT 469-59-0, Jervine 4449-51-8, Cyclopamine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(regulation of the hedgehog pathway and smoothened gain-of-function by gene patched agonists)

RN 469-59-0 CAPLUS

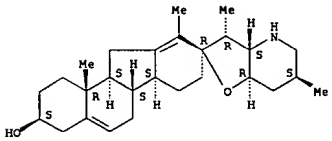
L4 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-11(1H)-one, 2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11a,11b-hexadecahydro-3-hydroxy-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



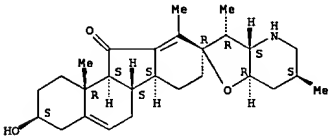
RN 4449-51-8 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 13 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:38438 CAPLUS
DOCUMENT NUMBER: 132:202865
TITLE: Effects of Veratrum nigrum alkaloids on central catecholaminergic neurons of renal hypertensive rats
AUTHOR(S): Li, Hua; Gao, Guang-You; Li, Shu-Yuan
CORPORATE SOURCE: Department of Pharmacology, Dalian Medical University, Dalian, 116027, Peop. Rep. China
SOURCE: Acta Pharmacologica Sinica (2000), 21(1), 23-28
CODEN: APSCG5
PUBLISHER: Science Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Aim: To study the central hypotensive mechanism of Veratrum nigrum L var ussurience Nakai alkaloids (VnA) in renal hypertensive rats (RHR). Methods: The quant. method of immunocytochem. (ICC) was used to observe and detect the effect of VnA (30 .mu.g .cntdot. kg-1, iv) on activity of central catecholaminergic (CA) neurons of C1, C2, A1, and A5 areas in RHR. Results: VnA increased the immunoreactivity (IR) of tyrosine 3-monooxygenase (TM)-immunopos. (IP) neurons of C1, C2, and A5 areas in RHR exptl. group compared with RHR control group [pos. units: (1.9.+-.0.4), (1.18.+-.0.23), (1.2.+-.0.4) vs (0.15.+-.0.22), (0.31.+-.0.16), (0.69.+-.0.20), resp.]; IR of TM-IP neurons of C1 and C2 areas in RHR control group was decreased compared with sham-operated group [pos. units: (0.15.+-.0.22), (0.31.+-.0.16) vs (1.45.+-.0.29), (1.36.+-.0.25), resp.]. Conclusion: VnA increased the activity of central CA neurons in RHR to exert its hypotensive effect.
IT **469-59-0**, Jervine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(Veratrum nigrum alkaloids effect on central catecholaminergic neurons in renal hypertension)
RN 469-59-0 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-11(1H)-one, 2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11a,11b-hexadecahydro-3-hydroxy-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

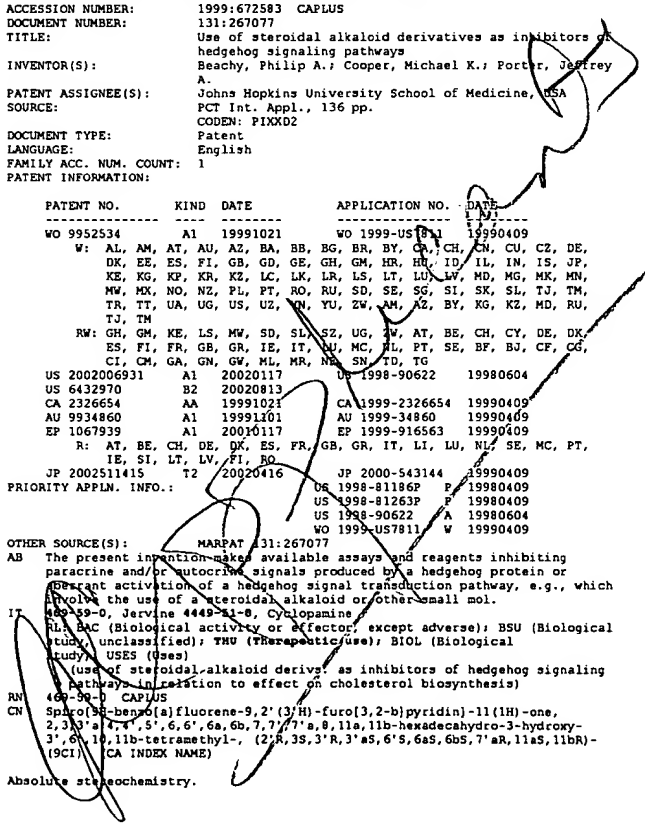
L4 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:672583 CAPLUS
DOCUMENT NUMBER: 131:267077
TITLE: Use of steroidal alkaloid derivatives as inhibitors of hedgehog signaling pathways
INVENTOR(S): Beachy, Philip A.; Cooper, Michael K.; Porter, Jeffrey A.
PATENT ASSIGNEE(S): Johns Hopkins University School of Medicine, USA
SOURCE: PCT Int. Appl., 136 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9952534	A1	19991021	WO 1999-US7811	19990409
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002006931	A1	20020117	US 1998-90622	19980604
US 6432970	B2	20020813		
CA 2326654	AA	19991021	CA 1999-2326654	19990409
AU 9934860	A1	19991101	AU 1999-34860	19990409
EP 1067939	A1	20010117	EP 1999-916563	19990409
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002511415	T2	20020416	JP 2000-543144	19990409

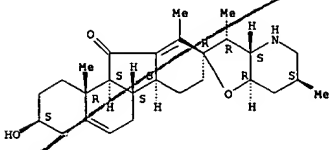
PRIORITY APPLN. INFO.: US 1998-81186P P 19980409
US 1998-81263P P 19980409
US 1998-90622 A 19980604
WO 1999-US7811 W 19990409

OTHER SOURCE(S): MARPAT 131:267077
AB The present invention makes available assays and reagents inhibiting paracrine and/or autocrine signals produced by a hedgehog protein or aberrant activation of a hedgehog signal transduction pathway, e.g., which involve the use of a steroidal alkaloid or other small mol.
IT **469-59-0**, Jervine **4449-51-8**, Cyclopamine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(use of steroidal alkaloid derivs. as inhibitors of hedgehog signaling pathways in relation to effect on cholesterol biosynthesis)
RN 469-59-0 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-11(1H)-one, 2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11a,11b-hexadecahydro-3-hydroxy-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

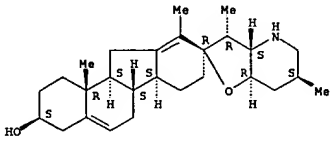


L4 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)



RN 4449-51-8 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

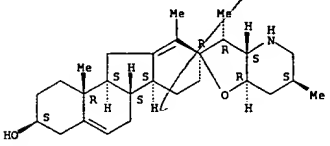
Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:639750 CAPLUS
DOCUMENT NUMBER: 131:331613
TITLE: A looking glass perspective: thalidomide and cyclopamine
AUTHOR(S): Gaffield, William; Incardona, John P.; Kapur, Raj P.; Roelink, Henk
CORPORATE SOURCE: Western Regional Research Center, ARS, USDA, Albany, CA, 94710, USA
SOURCE: Cellular and Molecular Biology (Paris) (1999), 45(5), 579-588
CODEN: CMOBEF; ISSN: 0145-5680
PUBLISHER: C.M.B. Association
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with many refs. Numerous naturally-occurring and synthetic compds. that were discovered initially because of their toxic properties, were later shown to possess biol. activities beneficial to humans that enabled them to serve as templates for the development of useful medicinal agents. A prominent example is thalidomide, a synthetic drug that gained notoriety originally due to its catastrophic teratogenicity in humans. The discovery of thalidomide's efficacy in treating several diseases has resulted in the recrudescence of the drug to society's usage. A current example of this phenomenon is the plant teratogen cyclopamine (11-deoxojervine), whose deleterious terata-inducing effects were restricted to grazing animals, but whose recently discovered inhibition of Sonic hedgehog signal transduction has provided both the potential to increase our understanding of organogenesis and to serve as a lead compd. in drug development.
IT **4449-51-8**, Cyclopamine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(thalidomide and cyclopamine)
RN 4449-51-8 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

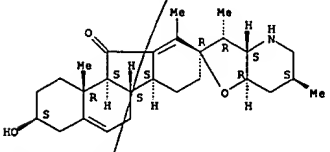


REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN (Continued)

L4 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:436553 CAPLUS
DOCUMENT NUMBER: 131:204460
TITLE: Steroidal alkaloids and stilbenoids from Veratrum taliense
AUTHOR(S): Zhou, Chang Xin; Tanaka, Junichi; Cheng, Christopher H. K.; Higa, Tatsuo; Tan, Ren Xiang
CORPORATE SOURCE: Institute Biotechnology, Department Biological Science Technology, Nanjing Univ., Nanjing, 210093, Peop. Rep. China
SOURCE: Planta Medica (1999), 65(5), 480-482
CODEN: PLMEAA; ISSN: 0032-0943
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phytochem. investigation of roots and rhizomes of Veratrum taliense yielded a new and six known steroidal alkaloids as well as a new and one reported stilbene deriv. By a combination of spectral methods (IR, MS, 1H- and 13C-NMR, COSY, HMQC, HMBC, and NOESY), the structure of the new alkaloid was established as 15-angeloylgermine while the known ones were identified as 15-(2-methylbutyroyl)germine, jervine, 3-veratroylzygadenine, germine, veramiline 3-O-.beta.-D-glucopyranoside and stenophylline B-3-O-.beta.-D-glucopyranoside. The new stilbenoid, named veraphenol, was detd. to be 2-(3',5'-dihydroxyphenyl)-6-hydroxybenzofuran, and the known one was shown to be resveratrol. The in vitro enzyme assay indicated that 3-veratroylzygadenine and resveratrol are inhibitors of xanthine oxidase. The enzyme inhibitory action of resveratrol, the most active compd. found so far in V. taliense, is dose-dependent with the IC50 value at 30 .mu.M (the IC50 value of allopurinol used as a pos. control in the study is 10 mM).
IT **469-59-0**, Jervine
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(steroidal alkaloids and stilbenoids from Veratrum taliense)
RN 469-59-0 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-11(1H)-one, 2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11a,11b-hexadecahydro-3-hydroxy-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

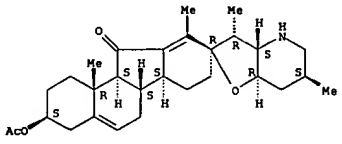
Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:686451 CAPLUS
DOCUMENT NUMBER: 123:102413
TITLE: O-acetyljervine: a new .beta.-adrenoceptor agonist from Veratrum album
AUTHOR(S): Gilani, Anwar; Aftab, Khalid; Saeed, S. A.; Ali, Rahat A.; Rahman, Atta-ur
CORPORATE SOURCE: Medical College, Aga Khan Univ., Karachi, 74800, Pak.
SOURCE: Archives of Pharmacal Research (1995), 18(2), 129-32
CODEN: APHRDQ; ISSN: 0253-6269
PUBLISHER: Pharmaceutical Society of Korea
DOCUMENT TYPE: Journal
LANGUAGE: English
AB I.v. administration of O-acetyljervine (an alkaloid from Veratrum album) produced a dose-dependent (10-100 .mu.g/kg) fall in blood pressure and tachycardia in anesthetized normotensive rats. Pretreatment of animals with propranolol (1 mg/kg) abolished these cardiovascular responses of O-acetyljervine similar to that of isoprenaline (1 .mu.g/kg). In isolated tissue expts., O-acetyljervine (10-100 .mu./mL) produced a dose-dependent relaxation of phenylephrine-induced contraction of the rabbit aorta. In guinea-pig spontaneously beating atria, it caused pos. inotropic and chronotropic responses in a dose-dependent fashion (10-100 .mu./mL). These responses were abolished in the presence of propranolol (1 .mu.g/mL) similar to that of isoprenaline. These results indicate that O-acetyljervine is a adrenoceptor stimulant (.beta.1 and .beta.2) like isoprenaline.
IT **14788-78-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(O-acetyljervine: a new .beta.-adrenoceptor agonist from Veratrum album)
RN 14788-78-4 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-11(1H)-one, 3-(acetyloxy)-2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11a,11b-hexadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 18 OF 18 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1972:108077 CAPLUS
DOCUMENT NUMBER: 76:108077
TITLE: Antiinflammatory activity of jervine
AUTHOR(S): Gerashchenko, G. I.; Bondarenko, N. V.; Semenchenko, V. F.
CORPORATE SOURCE: USSR
SOURCE: Aktual'nye Voprosy Farmatsii (1970), Volume Date 1968 169-71
CODEN: AKVFAM; ISSN: 0365-3811
DOCUMENT TYPE: Journal
LANGUAGE: Russian

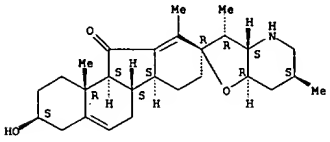
AB Jervine (I) [469-59-0] injected s.c. at 5 mg/kg/day 7 days into rats with a paw inflammation, induced by s.c. implanted cotton pellets, decreased the granuloma exudate and proliferation by 45 and 41%, resp., and the adrenal ascorbic acid [50-81-7] by 30%.

IT 469-59-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inflammation inhibition by)

RN 469-59-0 CAPLUS

CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-11(1H)-one, 2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11a,11b-hexadecahydro-3-hydroxy-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d ibib ab fqhit 1-3

L7 ANSWER 1 OF 3 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 134:295995 MARPAT
TITLE: Synthesis, compositions and uses of steroidal alkaloids as regulators of the hedgehog pathway
INVENTOR(S): Beachy, Philip A.
PATENT ASSIGNEE(S): Johns Hopkins University School of Medicine, USA
SOURCE: PCT Int. Appl., 164 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001027135	A2	20010419	WO 2000-US28479	20001013
WO 2001027135	A3	20020510		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1235851	A2	20020904	EP 2000-973544	20001013
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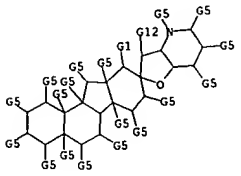
JP 2003516317	T2	20030513	JP 2001-530353	20001013

PRIORITY APPLN. INFO.: US 1999-159215P 19991013
US 2000-229273P 20000830
WO 2000-US28479 20001013

AB The present invention makes available, inter alia, methods and reagents for modulating smoothened-dependent pathway activation. In certain embodiments, the subject methods can be used to counteract the phenotypic effects of unwanted activation of a hedgehog pathway, such as resulting from hedgehog gain-of-function, ptc loss-of-function or smoothened gain-of-function mutations. Synthesis of cyclopamine, jervine and cycloposine derivs. is presented.

MSTR 8



L7 ANSWER 1 OF 3 MARPAT COPYRIGHT 2003 ACS on STN (Continued)

MPL: claim 7
NTE: or unsaturated forms, and/or seco-, nor- or homo-derivatives
NTE: additional substitution and ring formation also claimed

L7 ANSWER 2 OF 3 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 133:99549 MARPAT
TITLE: Regulation of the hedgehog pathway and smoothened gain-of-function by gene patched agonists
INVENTOR(S): Dudek, Henryk; Ji, Benxiu
PATENT ASSIGNEE(S): Ontogeny, Inc., USA
SOURCE: PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000041545	A2	20000720	WO 2000-US873	20000113
WO 2000041545	A3	20000928		
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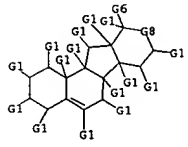
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6291516	B1	20010918	US 1999-417564	19991014
EP 1143961	A2	20011017	EP 2000-906910	20000113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2003517279	T2	20030527	JP 2000-593166	20000113
US 2001034337	A1	20011025	US 2001-867311	20010529

PRIORITY APPLN. INFO.: US 1999-115642P 19990113
US 1999-119594P 19990210
US 1999-142124P 19990702
US 1999-417564 19991014
WO 2000-US873 20000113

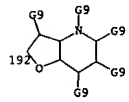
AB The present invention makes available methods and reagents for inhibiting aberrant growth states resulting from hedgehog gain-of-function, patched (ptc) loss-of-function or smoothened gain-of-function comprising contacting a cell with a compd., such as a polypeptide or small mol. in an amt. sufficient to control the aberrant growth state, e.g., to agonize a normal ptc pathway or antagonize smoothened or hedgehog activity. The present invention further makes available methods and reagents for ameliorating the consequences of hedgehog loss-of-function, ptc gain-of-function, or smoothened loss-of-function comprising contacting a cell with a compd., such as a polypeptide or small mol., in an amt. sufficient for amelioration. In certain embodiments, the subject compds., e.g., a cAMP analog, adenylate cyclase agonist, or cAMP phosphodiesterase inhibitor, regulate cAMP levels, which in turn modulates activity of the hedgehog pathway. Thus, compds. such as jervine, cyclopamine, and forskolin analogs are also effective in inhibition of medulloblastoma.

MSTR 18

L7 ANSWER 2 OF 3 MARPAT COPYRIGHT 2003 ACS on STN (Continued)



G8 = 192



MPL: claim 5
NTE: substitution is restricted

L7 ANSWER 3 OF 3 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 131:267077 MARPAT
TITLE: Use of steroidal alkaloid derivatives as inhibitors of hedgehog signaling pathways
INVENTOR(S): Beachy, Philip A.; Cooper, Michael K.; Porter, Jeffrey A.
PATENT ASSIGNEE(S): Johns Hopkins University School of Medicine, USA
SOURCE: PCT Int. Appl., 136 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9952534	A1	19991021	WO 1999-US7811	19990409
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002006931	A1	20020117	US 1998-90622	19980604
US 6432970	B2	20020813		
CA 2326654	AA	19991021	CA 1999-2326654	19990409
AU 9934860	A1	19991101	AU 1999-34860	19990409
EP 1067939	A1	20010117	EP 1999-916563	19990409
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002511415	T2	20020416	JP 2000-543144	19990409

PRIORITY APPLN. INFO.:
US 1998-81186P 19980409
US 1998-81263P 19980409
US 1998-90622 19980604
WO 1999-US7811 19990409

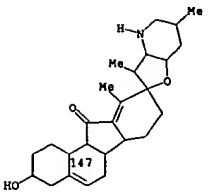
AB The present invention makes available assays and reagents inhibiting paracrine and/or autocrine signals produced by a hedgehog protein or aberrant activation of a hedgehog signal transduction pathway, e.g., which involve the use of a steroidal alkaloid or other small mol.

MSTR 1

G4—G1

G1 = 147

L7 ANSWER 3 OF 3 MARPAT COPYRIGHT 2003 ACS on STN (Continued)



MPL: claim 3

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L7            3 S L3 FULL
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